COOK®

Cook Group Incorporated

July 30, 2004

Ms. Lisa Rovin
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Docket No. 2004-N-0181

Dear Ms. Rovin:

This comment is filed on behalf of the Cook Group, Inc. ("Cook"), a holding company of international corporations engaged in the manufacture of diagnostic and interventional products for radiology, cardiology, urology, gynecology, gastroenterology, wound care, emergency medicine, and surgery. Cook pioneered the development of products used in the Seldinger technique of angiography, and in techniques for interventional radiology and cardiology. Cook products benefit patients by providing doctors with a means of diagnosis and intervention using minimally invasive techniques, as well as by providing innovative products for surgical applications. Cook sells over 15,000 different products which can be purchased in over 60,000 combinations.

We are submitting these comments in response to the request of the Food and Drug Administration (FDA) for input on activities that could reduce existing hurdles to medical product design and development. The agency has noted in its recently released report, "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," that there is an urgent need to modernize product development and to make the regulatory process more predictable and less costly. We agree with FDA, and we commend the agency for taking the initiative to highlight and explain this need in its report. We also thank the agency for seeking the input of all stakeholders.

As the FDA notes in its report, we are seeing unparalleled discoveries in basic science. These discoveries hold tremendous promise for treating patients around the world, yet they are not yielding actual, new medical products at the rate anticipated. As the report correctly states, "this is because the current medical product development path is becoming increasingly inefficient and costly." It is critical that we overcome this problem. Science is delivering undreamed of opportunities, and we must find the ways to take advantage of them.

750 Daniels Way – Bloomington, Indiana 47402
www.cookgroupinc.com

2004N-0181

C 16

We believe that through a broad dialogue, concentrated effort, and, in some instances, bold action, we can reverse the trend noted by the agency. Through constant focus on the needs of patients, hard work, and committed leadership from both the government and the health care industry, we can make significant progress. We set out some thoughts below for your consideration.

1. Fully exploiting available information.

In its recently released "Critical Path" report, FDA states: "agency reviewers see the successes and associated best practices as well as the failures, slow-downs, barriers, and missed opportunities that occur during the course of product development. In addition, data on product testing, safety evaluation and critical trials are stored in millions of pages of FDA files."[1]

The value of all of this experience and information to science, product development, and the approval of products is incalculable. Determining how to access it, organize it, and utilize it is a Herculean task, yet we believe this should be a top, long-term priority of the agency.

As FDA addressees the use of information, it will be necessary for it to work with stakeholders to make clear what information is available and how it might be used. The agency will need to address the information technology resources that will be needed and to develop consensus on very sensitive issues involving privacy and proprietary information. This will be a difficult and time consuming task. Cook recommends that FDA begin by convening a series of stakeholder meetings to discuss all of the implications. Representatives from the Centers of Medicare and Medicaid Services (CMS), the National Institutes of Health (NIH), and the Center for Disease Control (CDC) should be invited. So, too, should other organizations such as the Regenstrief Institute of Indiana. All of these institutions possess important databases that are relevant to the process of technology development and expertise on how to utilize them. These other organizations could host their own meetings as well and invite representatives of FDA to participate. Such activities would be a natural follow-on to the Secretarial Summit on Health Information Technology held earlier this month.

---

[1]US Department of Health and Human Services, Food and Drug Administration, "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," March 2004, page 13.

One mechanism for sharing this information may be for the agency to issue early non-binding guidance for new product types, initially outlining science-based considerations for establishing new performance criteria, and ultimately resulting in a final guidance document. The key is to provide guidance to industry early in the development phase based on information available to FDA, such as appropriate bench testing and animal models, in order to streamline the process and avoid duplication of the same science by numerous companies.

We believe that fully utilizing data available to FDA can have immense benefits. If the focus is on the needs of the patients, we believe success can be achieved. The medical and scientific communities and industries which develop medical technology can bring new discoveries to patients much more rapidly if we take advantage of the tremendous amount of information that could be made available, rather than individually determining requirements and conducting duplicative studies. Further, we can save significant resources and time if we do not require all sponsors of new products to address technical questions over and over again when the answers to those questions have been well established and are well known by FDA.

2. International Harmonization

The market place for medical technology has truly become global. As developers of new products determine whether to pursue a new concept, one of the first questions they must address is whether the products can win approval under the various regulatory systems that exist around the world and, if so, whether such approvals can be obtained at a reasonable cost and in a reasonable time frame. In some instances, promising new ideas are abandoned because of the complexity and cost of dealing with multiple regulatory regimes. In almost all cases, the cost of new technologies is significantly higher than it would be were there one regulatory system.

In 1992, the Global Harmonization Task Force (GHTF) was established to address these issues and to attempt to bring regulatory systems together. GHTF has made an important contribution in harmonizing some regulatory concepts, but the problems created by multiplicity of regulatory systems are growing, not shrinking. The major nations that comprise GHTF have been reluctant to make real changes in their own systems. While they have produced a series of documents recommending model regulatory processes, they, for the most part, have not adopted those documents themselves. Ironically, these models have been appropriated by smaller countries, spurred on by the prospect of revenues from user fees. New regulatory bureaucracies, based on GHTF models or variations of them, are growing up in countries around the world that previously accepted products approved in any of the GHTF nations.

We believe this trend must be reversed. Resources needed to develop technology should not be squandered to meet scores of different regulatory requirements that could be harmonized.

We recommend that international harmonization be made a high priority and that the United States provide the leadership necessary to invigorate the harmonization effort. Patients around the world cannot afford to have this effort move at a snail's pace. It is time to move forward boldly, and that means a commitment from the top in the Unites States government and the medical technology industry.

3. Proof of Concept

As the "Critical Path" report notes, "For very innovative and unproven technologies, the probability of an individual product success is highly uncertain, and risks are perceived as extremely high. Often, bench tests, computer modeling, and animal studies provide only a modicum of relevant information. Significant questions remain unanswered, and the agency is left with a quandary in determining whether and how to move forward with the product."[2]

In the long term, government and industry must invest in better technologies and better indicators regarding the potential safety and utility of new medical technologies. There is much more work that should be done to develop the potential of computer modeling, for example. Bayesian statistics and other advanced statistical concepts render it easier to extrapolate results form a small patient population to the population as a whole. Wherever possible we should seek to utilize the newest testing methods to minimize the need for testing in humans and, indeed, to minimize the sacrifice of animals.

In the short term, however, it is important that FDA resist the temptation to order more and more bench tests, computer models, or animal studies that have little promise to yield additional relevant information about whether a product is safe and effective. Instead, the agency must engage in a realistic determination for each product regarding the value of information that can be gained from such studies or available computer models. Then it must undertake an objective risk/ benefit analysis to determine if it is appropriate to allow limited use of the product in humans, focusing on pre-clinical safety information rather than efficacy.

---

[2] Ibid, page 8.

We suggest that FDA make this determination early on in the process, and in appropriate instances, permit limited proof of concept trials in humans. This is especially true where the therapy is for patients for whom no acceptable medical treatment is available.

As it works with those developing new technologies, FDA should recognize that proof of concept trials should be an integral part of the development and learning process. Negative experiences in such trials may provide the precise information that is needed to modify a procedure or the design or material used for a product and ultimately bring tremendous benefit to patients. We must not abandon promising discoveries because of early failure, or when satisfactory outcomes cannot be guaranteed.

4. Clarity for Combination Products

Advances in basic science are leading to the design and development of products that require thoughtful consideration regarding the most appropriate route for regulatory review. These products often combine various aspects of biologics, devices, and pharmaceuticals. As FDA charts the "critical path" for combination products, the agency needs to clarify the approval process for such novel products.

While amendments in both the Safe Medical Devices Act of 1990 and the Food and Drug Administration Modernization Act of 1997, as well as in the recently enacted Medical Device User Fee and Modernization Act of 2002, were intended to define the appropriate regulatory category for combination products and the appropriate centers for their review, we are concerned that FDA is currently losing sight of statutory definitions. If it continues to do so, it will cause great confusion as to how these products are to be regulated and, in the end, result in significant delays in the approval of new and exciting technologies.

Specifically, the agency appears to be taking the position that combination products have become a fourth type of product and that they constitute a new regulatory category. Further, the agency seems to believe that it has unlimited discretion to regulate combination products in a new system. As a result, the agency is mixing and matching regulatory authorities for various aspects of the regulatory process despite the fact that combination products are legally single entities, i.e., drugs, devices, or biologics products. If this approach continues to be followed, we believe it will lead to an unauthorized, complex, and cumbersome regulatory structure.

We recommend that FDA re-examine its approach to combination products and correct its course. Combination products are not a separate jurisdictional category. They must be regulated as drugs or devices, or biological products. These products are assigned to a center based upon primary mode of action. This assignment should govern a product's premarket and postmarket regulation. The appropriate center may consult with other centers if additional expertise is needed. Furthermore, we note that the device regulations with their flexibility, comprehensiveness, and emphasis on design controls in product development and manufacturing are well suited to the regulation of combination products which have the primary mode of action of a device.

5. Defining a Path for Tissue Engineered Products

An interagency working group composed of members from NIH, FDA, the Department of Defense, NASA, the Department of Commerce, and the National Science Foundation has proposed the Federal Initiative for Regenerative Medicine ("FIRM") as an overarching program of funding, governance, and milestones to encourage the availability of tissues and regenerated organs on demand in twenty years, with interim goals for availability of products such as complex skin, cartilage, and bone substitutes in five years, and tissue and organ patches to help regenerate damaged kidneys, hearts, and other organs in ten years. The FIRM program recognizes "the obvious health benefits" of such technologies, as well as the fact that regenerative medicine "is desperately needed to combat rising healthcare costs."[3]

Unfortunately, the regulatory path to approval is not marked clearly in this area. Many tissue engineered products are combination products that have the primary mode of action of a biologic, but with clinical outcomes measures similar to devices. Where a product is legally a biologic, that has the characteristics of a device, the agency must take care to avoid overregulation while assuring safety and effectiveness.

---

[3] Interagency Federal Working Group on Regenerative Medicine, *2020: A New Vision, Federal Initiative for Regenerative Medicine,* January 2004 Draft, page 1.

To expand, many tissue engineered products are more device like than biologic like in development, structure, and in use, and are subject to the medical device market realities of small markets, slow adaptation, higher manufacturing costs, and lower growth margins. Thus it is essential that FDA take a fresh look at appropriate regulation of such technologies under the Public Health Service Act. We believe the inherent flexibility of standards for licensing, and in particular for potency, allow FDA to craft rational pathways for tissue engineered products that resemble, as appropriate, the market approval requirements for class III medical devices.

In particular, we advocate the following basic principles as highly desirable in an approval pathway for such products:

- An approval pathway should be defined and developed which allows these products to come to market in a time-frame consistent with representative class III devices.

- The standard for efficacy trials should parallel those used for contemporary class III medical devices.

- Historical standards of care, having sufficient detail regarding methods and outcomes, should be acceptable in most instances as a control in efficacy trials, and requirements for placebo control should be rare.

- No requirement for metabolism, distribution, or excretion studies, or phase I or phase II clinical trials should be imposed, and potency requirements should appropriately reflect product characteristics and indications for use.

- Safety and purity tests for living components of these devices should be equivalent to those required for other forms of transplanted tissues and cells, e.g., FDA's anticipated rules on current good tissue practices and donor suitability.

For example, the clinical data requirements for approval of a bio-artificial liver that is intended to act as a bridge to transplant (e.g., liver cells lining a device substrate through which a patient's blood flows for cleansing and other hepatic functions), should not require large numbers of patients or placebo controls. Because the disease progression in liver failure is predictable, the effects should

be obvious and a historical control should suffice; indeed, the patient's stage of disease at the point of necessary intervention can establish a baseline and serve as

a control in and of itself. A historical control is recognized under the device regulations as a valid basis for quantative comparison between the test product and the control,[4] and should suffice for device-like biologics that meet the criteria of the regulation. The length of the trial should reflect the expected time to transplant. Likewise, the number of patients should reflect the predictability of disease progression and risk of non-treatment, rather than a patient population that may rule out unlikely side effects. Safety requirements should encompass those for any other similar tissue or cellular product regarding donor and product screening for communicable diseases. Product testing requirements for safety, purity, and potency should reflect what is practical and necessary with respect to product characteristics and the manufacturing process.

We further believe that both FDA and industry would benefit from a collaborative working group that would evaluate two or three different types of tissue engineered products, the appropriate regulatory requirements for scientific and clinical evidence to support their approval, and the appropriate approval pathways. We would suggest a group under the auspices of the FDA, specifically including representatives of CDRH and CBER as well as expert scientists, previous panel members, engineers, researchers, and physicians from a variety of public and private organizations involved in the development, study, and regulation of tissue engineered products. We believe that such a forum can lead to guidance that will result in the definition of a regulatory path that will assist in bringing these critical product categories to the market.

6. Refurbishing the approval process for medical devices.

If we are to bring new products to patients in the most effective manner, we believe that the process for approving medical devices, should be constantly reviewed and improved. Experience brings knowledge. We often learn that things we thought were important to the regulatory process really are not. These extraneous requirements can be eliminated, or minimized. We also learn that other elements in the process provide more value than we had previously recognized. These core requirements need to be emphasized. We set out below areas where we believe improvements can be made in the current process:

[4] 21 CFR 860.7(f) (1) (iv) (d).

a. Reclassification and Exemption

When products are new, there are many questions that need to be answered about them, and they merit careful scrutiny. After products are in the marketplace for a number of years, however, the questions are often answered. There are few issues for FDA to consider in determining whether such products should be approved, other than the sponsor's adherence to quality systems. Coronary angioplasty balloons, for example, no longer raise the questions for approval that they did when they were initially introduced.

Similarly, many class II products do not raise issues that need to be considered in the 510(k) process, and, in many instances, that process has become a shuffling of paper. We believe that industry and FDA should not squander resources executing clerical tasks which do not contribute to the public health. Those tasks should be eliminated so that resources can be focused on the exciting discoveries that FDA so aptly describes in the "Critical Path" report.

To accomplish this, we recommend that FDA periodically conduct an internal review of class II products and take the steps to exempt those which do not require premarket scrutiny. It should also review class III products on a regular basis, and work to reclassify them so that regulatory resources can be shifted to products which require an enhanced level of scrutiny. In addition, FDA should request industry recommendations for devices that can be downclassified or exempted. Such exemptions and reclassifications should be very beneficial to the process, but it should be emphasized that they will occur only if FDA makes the necessary internal reviews a priority.

b. Changes in IDE's

In 1997, Congress enacted a procedure to give sponsors who have Investigational Device Exemptions (IDE's) latitude in making minor changes to study protocols or to devices themselves, if those changes do not affect the validity of the study or the basic operation of the device. This provision was placed in the law because Congress recognized the evolutionary nature of device development. During the product development process, sponsors often gain information which requires minor changes, and they should be able to make those changes without unduly delaying the progress of their studies.

Unfortunately, this provision has not worked well. IDE supplements continue to number more than 4,000 per year, and processing them consumes significant resources, from both an agency and an industry perspective. We recommend that the FDA work with industry to clarify this process so that it can save additional resources that can be dedicated to exciting new products.

c. Postmarket Surveillance

Premarket studies are very important. They do not, however, resolve all of the issues that a new technology will face when it is mass produced and introduced to thousands of doctors and to the general patient population.

Further, premarket studies that conclusively demonstrate clinical effectiveness can be extremely expensive and time consuming. In some instances, FDA has utilized surrogate endpoints to hasten the dispersion of badly needed technologies for which there are no alternatives, and then used post market surveillance and post market studies to demonstrate effectiveness. While expectations for these studies need to be fully defined, we believe that this is a wise approach that should be utilized frequently by the agency in moving new technologies to patients. To facilitate this practice, FDA and industry should develop an agreed upon mechanism to ensure that the postmarket studies or surveillance are indeed conducted. It should be noted that postmarket surveillance, a careful monitoring of the use of a new technology, can often be more valuable than extensive studies.

As we develop ways to effectively utilize information, databases assembled by CMS, NIH, and other organizations can also be extremely valuable in postmarket analysis. They can add tremendously to the follow on studies typically done after approval of a new technology.

d. Off-Label Use

Many medical technologies are used today for off-label purposes, particularly in treating small patient populations. Physicians often collect significant data regarding the safety and effectiveness of such off-label uses. Unfortunately, the law constrains FDA in considering data gained from off-label use in applications for approvals for uses. We recommend that FDA undertake a legal analysis of these constraints to determine if they can be removed. To the extent that a statutory change is required, we recommend that FDA propose legislation to Congress to permit the utilization of such data with appropriate safeguards to ensure against abuse by manufacturers. Utilizing such data can significantly expedite the approval of new conditions of use for important technologies, particularly for small patient populations.

e. Indications for Use

Over the course of the last decade, we have observed a tendency at FDA to consistently narrow the conditions of use in the approval process. Often there are several reasonably implied uses other than the primary indication as defined by FDA that are quickly recognized and adopted by physicians. These uses do not involve significant risks, but they are technically "off-label," and present problems such as those described above. This could also be avoided if FDA reversed the trend towards ever narrower conditions of use and approve the broadest possible indications for use.

f. Advisory Panels

Advisory panels assist the FDA in considering premarket applications. These panels provide valuable expertise to the agency. Occasionally, however, members are not well informed about the new products before them. It is important that steps be taken to communicate early on with the members of the panels and clearly identify issues of interest to maximize the panels' value.

g. Institutional Memory

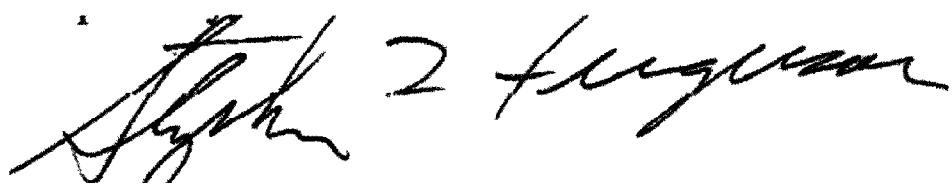
As FDA notes in its reports, the experience of its reviewers is a great asset. Reviewers remember what succeeded or what did not succeed, and what is needed or what is not needed. Care must be taken not to adopt additional regulatory requirements simply because no one remembers what happened in the past, and maintaining longevity of service is a goal that the agency must continue to foster by retaining the most dedicated and accomplished employees. These valuable people maintain the history and tradition of the FDA, and they are the agency's institutional memory. One of the most important functions that management can perform is to make certain that all possible steps are taken to minimize staff turnover so that the value of this asset does not depreciate.

We hope that these suggestions are helpful to the FDA as it considers the steps needed to improve the product development process. We have attached as Appendix A a matrix which provides a summary of the key features of a process that we believe we should be working towards.

We again congratulate the agency for taking this initiative, and we express our gratitude for its leadership. We are also heartened by the establishment in the Department of Health and Human Services of the Task Force to Encourage Medical Innovation. In establishing this task force, Secretary Tommy Thompson has further underscored the opportunities and challenges that science brings to our nation. It is critical now that stakeholders, including leaders in government, industry, medicine, and health care build on the momentum that HHS has initiated. Together we must engage in the hard work that is needed to meet the challenges of providing exciting, new medical technologies to American patients in a timely fashion.

Thank you for consideration of our views.

Respectfully,



Stephen L. Ferguson

APPENDIX A
"THE CRITICAL PATH REDEFINED: TOWARDS A DYNAMIC DEVELOPMENT AND APPROVAL PROCESS FOR MEDICAL TECHNOLOGY"

Stage in Product Development Cycle	Relevant Steps
Early Development	• Utilization of databases (FDA, NIH, CMS, CDC, Other). • Utilization of standards.
Early Testing	• Bench testing. • Advanced computer modeling. • Other new testing methods. • Animal testing.
Investigation	• Definition by FDA and sponsor of meaningful endpoints and study protocol based on all information available to FDA and sponsor. • Development of objective performance criteria by product types based on all information available to FDA. • No proof of known principles required. • Employment of proof of concept trials where appropriate. • Acceptance of foreign data. • Utilization of most advanced statistical analysis, including Bayesian analysis where appropriate. • Maximum use of historical data. • Development of data appropriate for all jurisdictions in an internationally harmonized system.
Approval	• Risk/benefit analysis. • Postmarket study or surveillance where appropriate; using sites of original clinical trials and using all applicable databases.
Regulatory Principles	• Downclassification or exemption of products that have become low risk products. • Categorization of combination products according to PMOA and regulation of these products accordingly. • Recognition of flexibility under the PHS in regulating tissue engineered products.